REMARKS

This responds to the Office Action mailed on February 28, 2006, and the references cited therewith.

Claims 19 and 20 have been added. As a result, claims 1-3, 5-10 and 12-20 are now pending in this application.

Claim 19 contains the language of claim 1 without the phrase "where said peptides comprise immunodeficiency retroviral Gag, Gp120, Nef or Pol peptides." Applicants submit that this claim language is essentially identical to the language of original claim 1. Therefore, no written description or new matter issue can arise.

Claim 19 is added in view of recently published data from the inventors showing that improved protection can be obtained when administering a recombinant virus that encodes a wide spectrum of antigens. Thus, as stated by the inventors, the breath of the immune response is probably more important than high frequency response to a limited number of epitopes (see Hel et al., Abstract). Hel et al., *Improved Vaccine Protection from Simian AIDS by the Addition of Nonstructural Simian Immunodeficiency Virus Genes*, J. Immunol. 176: 85-96 (2006) (submitted herewith in a Supplemental Information Disclosure Statement).

Claim 20 contains the language of claim 1 with the phrase "where said peptides comprise immunodeficiency retroviral Gag, Pol, Env peptides or a combination thereof." Applicants submit that this claim language is essentially identical to the language of original claim 1 and that the Examples illustrate use of a recombinant virus that can express Gag, Pol, Env peptides or a combination thereof. Therefore, no written description or new matter issue can arise.

Claims 1 and 18 are amended. The term "structural" has been deleted from claim 1. Although supported by the specification, use of the term "structural" was not present in original claim 1. Thus, removal of this term from claim 1 adds no new matter. Language relating to maintaining a reduced viral load has been added to clarify the subject matter of claim 18. Support for this embodiment can be found throughout the specification as filed, for example, in Example 1 (see, e.g., page 22, lines 10-12) and Figure 1.

Applicants submit that no new matter has been added to the specification.

§112, Second Paragraph, Rejection of the Claims

Claims 1-3, 5-10 and 12-18 were rejected under 35 U.S.C. § 112, second paragraph, as allegedly indefinite with respect to the following issues.

A protective CD8+ HIV structural antigen response

The Examiner alleges that the phrase a "protective CD8+ HIV structural antigen response" is indefinite because some of the HIV specific peptides are non-structural antigens. The term "structural" has been deleted from independent claims 1 and 18. Applicants request withdrawal of this rejection under 35 U.S.C. § 112, second paragraph, with respect to language relating to the "protective CD8+ HIV antigen response."

Viral load

The Examiner alleges that claim 18 is indefinite because the preamble calls for a reduced viral load but claim 18 is directed to a method of treating patients who already have a reduced viral load. According to the Examiner, it is not clear if the claims are directed to reductions in viral load, maintenance of low viral loads or prevention of rebounding viral loads after cessation of antiviral administration or after development of drug-resistant variants.

Claim 18 is now directed to "maintaining a reduced viral load" in a mammal. Support for this embodiment can be found throughout the specification as filed, for example, in Example 1 (see, e.g., page 22, lines 10-12) and Figure 1. Applicants request withdrawal of this rejection under 35 U.S.C. § 112, second paragraph, with respect to language relating to viral load.

Viral load and protective CD8+ HIV antigen response:

The Examiner alleges that claim 18 is indefinite because this claim calls for a reduction of viral load in the preamble and specifies that the immunodeficiency retroviral specific peptides are presented in an amount sufficient to stimulate a protective $CD8^+$ HIV antigen response. According to the Examiner it is not clear whether the claim is directed to generating a HIV-1-specific CTL response or reducing viral load.

As indicated above, claim 18 is now directed to "maintaining a reduced viral load" in a mammal. Moreover, claim 18 further recites that the peptides are presented in an amount

sufficient to stimulate a protective $CD8^+$ HIV antigen response and thereby maintain a reduced viral load in the mammal. Support for this embodiment can be found throughout the specification as filed, for example, in Example 1 (see, e.g., page 22, lines 8-13) and Figures 1 and 4.

Applicants submit that the language of claim 18 is definite and requests withdrawal of this rejection under 35 U.S.C. § 112, second paragraph, with respect to the language of claim 18.

§112, First Paragraph, Rejection of the Claims

Claims 1-3, 5-10 and 12-18 were rejected under 35 U.S.C. § 112, first paragraph, as allegedly lacking enablement. According to the Examiner, the specification fails to enable the following.

Guidance pertaining to the correlates of human protection

The Examiner has asserted that the disclosure fails to provide any guidance pertaining to the correlates of human protection. In particular, the Examiner has stated that it is not clear whether the CD8+ T-cell response is protective or therapeutic and whether cytotoxic T cells are responsible for the protection/therapy.

Applicants first submit that the application as filed has five Examples showing that the invention has successfully been performed in a recognized animal model of HIV-1 infection. As described by The NIAID Division of AIDS, use of macaque monkeys infected with simian immunodeficiency virus (SIV) comprise a useful animal of model HIV infection because SIV in macaques follows a similar disease course to HIV (The NIAID Division of AIDS, *Animal Models,* http://www.niaid.nih.gov/daids/vaccine/animals.htm (Feb. 10, 2003); previously submitted in an Information Disclosure Statement).

Second, Applicants have previously provided evidence that the statements in the application as filed are correct and the treatment methods are useful in humans. In particular, Applicants have submitted a Declaration by Dr. Franchini (with the May 16, 2005 Response) providing preliminary results from a clinical trial indicating that human patients who received the recombinant vCP1452 pox virus alone had a lower viral load than those who received placebo (page 5 of the Declaration Appendix)). In the Quest trial, patients who received the

recombinant pox virus also had increased CD4 and CD8 responses at week 24 (see page 11 of the Declaration Appendix).

Third, the utility of the present methods for human treatment is further illustrated in Jin et al. (J. Virol. 76: 2206-16 (2002), previously submitted in an Information Disclosure Statement), which shows that administration of the ALVAC vCP1452 recombinant virus stimulates an HIV1-specific $CD8^+$ response in HIV-infected patients who have been receiving antiretroviral therapy. Note that the vCP1452 recombinant virus is the same as the recombinant virus referenced in the Declaration by Dr. Genoveffa Franchini filed on May 16, 2005. The recombinant vCP1452 virus is a recombinant pox virus that encoded gp120, gp41, p55, pol and nef HIV peptides (*id.* at page 2207). Patients included in the study described by Jin et al., were infected with HIV but had a viral load of 50 copies HIV-1 RNA per ml plasma and an average CD4 count of 779 (see page 2207). As stated at page 2211 of the Jin et al. article, 78% of patients had an increase in $CD8^+$ T-cell responses to at least one HIV-1 antigen (see also Figure 4b and pages 2213-14). Thus, the methods of the invention do stimulate CD8+ responses in humans.

Fourth, Applicants submit that contrary to the Examiner's assertion that the specification does not provide guidance on which viral epitopes to use, Applicants submit that the specification clearly teaches that a variety of epitopes can be used (see, e.g., page 11, lines 6-20). Moreover, statements made in the specification about the selection of HIV epitopes are supported by an article recently published by the inventors, Hel et al., *Improved Vaccine Protection from Simian AIDS by the Addition of Nonstructural Simian Immunodeficiency Virus Genes*, J. Immunol. 176: 85-96 (2006) (submitted herewith in a Supplemental Information Disclosure Statement). The Hel et al. publication provides data showing that administration of a combination of structural and non-structural antigens leads to a delay in the onset and a decrease in the extent of viremia in macaque monkeys upon challenge with simian immunodeficiency virus. Hence, as stated in the present specification at page 11, lines 11-13, structural and non-structural HIV-specific peptides can be used in the present methods. Moreover, as disclosed by the inventors in the Hel et al. article: "[T]he breadth of the immune response is probably more important than high frequency responses to a limited number of epitopes" (see, Hel et al. Abstract).

Applicants submit that sufficient correlates of human protection are provided by the specification and requests withdrawal of this rejection with respect to the correlates of human protection.

HIV vaccines frequently fail because of the "quasispecies" nature of HIV infection.

The Examiner asserts that HIV exists as a large pool of genotypically and phentypically distinct isolates and that the plasticity of the HIV contributes to its escape from immunological attack.

Applicants submit that the failure experienced by researchers in the past was due to use of traditional protein-based or peptide-based vaccines that relied upon induction of humoral immunity, usually to specific narrow HIV epitopes. See, e.g., Sauter et al., *Non-Replicating Viral Vector-Based AIDS Vaccines: Interplay Between Viral Vectors and the Immune System*, CURR. HIV RES. 3: 157-181 (2005) (previously submitted in an Information Disclosure Statement).

In contrast to the failed humoral-based vaccines of the past, the present invention relies upon generating cellular immune ($CD8^+$) responses to a variety of HIV epitopes. Thus, the specification demonstrates that a $CD8^+$ response is elicited in an accepted animal model (macaques) when a recombinant virus is administered, which enters the cells of the animal and intracellularly produces HIV-specific peptides (see Examples).

Applicants submit that the claimed use of a recombinant virus overcomes the failures of the past. Proof that the inventive use of such recombinant viruses provides a heightened immune response is provided throughout the article published by Sauter et al. (2005). For example, as stated in the Abstract of Sauter et al. (2005), "recombinant viral vector-based HIV vaccines [are] capable of eliciting both cellular and humoral immune responses." Sauter et al. (2005) further states the following in the Abstract.

> These new viral vector-based vaccines encoding multiple HIV antigens, delivered either alone or in heterologous prime-boost modalities elicited antigen-specific CTL responses in immunized hosts and protected animals from disease. The viral vector-based vaccines have proven to be potent vaccines in pre-clinical studies and foster the hope to put an end to the ever-increasing threat of the AIDS epidemic.

> Several unique features of viral vector-based HIV vaccines have contributed to their success, including their intrinsic immune-modulating properties, high transduction efficiency, and *in vivo* production of immunogens within the cell mimicking a natural infection without the associated health risks.

In addition, other articles published since the filing date of the application confirm that administration a vaccine comprising antigens from one clade are effective against HIV infections of another clade. For example, Smith et al., has shown that vaccination with HIV-1 antigens from one type of HIV-1 elicit a good CD8 response when animals are infected with a different strain or clade HIV (*Studies in Macaques on Cross-Clade T Cell Responses Elicited by a DNA/MVA AIDS Vaccine, Better Conservation of CD8 than CD4 T Cell Responses*, AIDS Res. & Hum. Retrovir. 21: 140-44 (2005)). The DNA and recombinant viral vaccines employed expressed Gag, Pol and Env proteins of HIV-1 (clade B). *Id.* at 141. As demonstrated by Smith et al., this clade B vaccine elicited a CD8 immune response in animals and this CD8 response was also responsive to HIV-1 clade A/G peptides. *Id.* at 141-42. As stated by Smith et al. in the Abstract, these studies "revealed essentially complete conservation of the CD8 response but only ~50% conservation of the CD4 response." See also, Amara et al., *Studies on the cross-clade and cross-species conservation of HIV-1 Gag-specific CD8 and CD4 T cell response elicited by a clade B DNA/MVA vaccine in macaques*, Virology 334:124-33 (2005)(previously submitted). Thus, a vaccine against one HIV-1 clade can be used to induce a significant CD8 response and, upon exposure to HIV Gag and Env peptides of another clade, essentially 100% pf CD8 T cells respond. These data indicate that the present methods do stimulate a CD8 response and are generally applicable to a variety of HIV types even if the methods involve administration of antigens of a single clade-type.

Applicants request withdrawal of this rejection with respect to the quasispecies nature of HIV.

Guidance as to those immunogens that confer protection

The Examiner has alleged that the specification fails to provide guidance as to the molecular determinants modulating protective immune responses, and urges Applicants to identify the epitopes that give rise to a protective or therapeutic immune response.

Applicants submit that the Examiner is focused on prior art problems that have been overcome by the use of recombinant viral vectors. In particular, as described by Sauter et al. (2005), traditional protein-based vaccines are not as effective as is administration of the present recombinant viral vectors. Thus, Applicants have moved away from identification of specific protein epitopes and or antigens that were formerly used without success, and have provided, instead, a new recombinant viral vector-based method that permits expression (and therefore administration) of a large variety of HIV-specific peptidyl sequences.

Moreover, as indicated by the inventors in their recent publication, incorporation of a broad spectrum of HIV sequences into the administered recombinant virus improves the immune response and leads to enhanced protection against HIV infection. See, Hel et al., *Improved Vaccine Protection from Simian AIDS by the Addition of Nonstructural Simian Immunodeficiency Virus Genes*, J. Immunol. 176: 85-96 (2006). Thus, as described by the inventors in the Hel et al. article: the breath of the immune response is probably more important than high frequency response to a limited number of epitopes (see Hel et al., Abstract).

Applicants submit that the claims are properly directed to a broad spectrum of HIV antigens, because such a broad spectrum of antigens is more effective than would be a limited number of epitopes. Applicants request withdrawal of this rejection with respect to the scope of immunogens.

Working embodiments

The Examiner asserts that the only example relating to humans provided in the specification is a prophetic example that does not provide meaningful data and that the macaque animal model is not an art-recognized model for vaccine development. In support of these assertions, the Examiner cites to articles published by different authors.

Applicants submit that the application does provide data showing the beneficial effects of the present methods in an accepted animal model of HIV infection (macaque infection with virulent SIV_{251}, see Examples 1, 3, 4, 5 and 6) and that a preponderance of evidence exists showing that macaques are a recognized animal model not only for HIV studies but for vaccine development in general.

Thus, for example, the following recent articles indicate that macaques are a good animal model for development of human vaccines. *See, e.g.*, Sun et al., *Protection of Rhesus monkeys against dengue virus challenge after tetravalent live attenuated dengue virus vaccination*, J. INFECT. DIS. 193(12): 1658-65 (June 15, 2006); Philipp et al., *Experimental infection of rhesus macaques with Streptococcus pneumoniae: a possible model for vaccine assessment*, J. MED. PRIMATOL. 35(3): 113-22 (June 2006). Note that, Philipp et al. (2006) states that the "macaque species serves as a major model for immune function of humans" (page 11, left column).

Moreover, the International AIDS Vaccine Initiative reports that the old antibody-induction approach to solving the HIV infection is flawed and that new approaches that involve stimulating $CD8^+$ responses employing, for example, recombinant viral vectors and utilizing testing in SIV and macaques are needed to develop an effective treatment for HIV (Freidrich & Watkins, *The role of the SIV model in AIDS vaccine research*, IAVI REPORT 9(2) (June 14, 2005)(downloaded Aug. 24, 2005 from http://www.iavireport.org/Issues/Issue9-2/Perspective.asp)(submitted herewith).

Similarly, as described by The NIAID Division of AIDS, use of macaque monkeys infected with simian immunodeficiency virus (SIV) comprise a useful animal of model HIV infection because SIV in macaques follows a similar disease course to HIV (The NIAID Division of AIDS, *Animal Models,* http://www.niaid.nih.gov/daids/vaccine/animals.htm (Feb. 10, 2003); previously submitted in an Information Disclosure Statement).

Thus, several authoritative sources have found that macaques are a good animal model for human immune function.

Moreover, the SIV_{251} strain is a highly virulent strain of SIV, leading to development of AIDS in substantial numbers of macaques within one year of infection. *See*, Lu et al., J. Viol. 70: 3978 (1996) (provided in a Supplemental Information Disclosure filed herewith).

Applicants submit that there is ample evidence demonstrates that results obtained in macaques using virulent strains of SIV are applicable to humans. Applicants request withdrawal of this rejection with respect to the working embodiments provided in the application.

Unpredictability in the State of the Art

The examiner has alleged that there is not a single effective HIV CTL vaccine on the market and that while several clinical trials have been conducted, in every situation the immunogen failed to induce long-lasting and high-titer immune responses. The Examiner further alleges that enablement must be established as of the filing date of the application and publications dated after the filing date of the application cannot be used to show what was known at the time of filing.

Applicants assert that the methods described and illustrated in the application are fully enabled because they clearly stimulate a HIV1-specific $CD8^+$ response. This has been shown by Applicants not only in the application as filed (see Examples) but also subsequent studies performed by the inventors and others, not only in animal models but also in humans. Thus, Applicants have provided evidence that the present methods do produce a CD8+ response in humans by submitting the Franchini Declaration (filed May 2005), and by providing publications showing that the present methods are effective for producing a CD8+ response in humans (see, e.g., Jin et al. (J. Virol. 76: 2206-16 (2002)).

Moreover, Applicants submit that articles published after the filing date are highly probative of the statements made in the application and claims. In particular, such post-filing publications provide evidence that the statements made in the application and the methods described in the application are, in fact, true. Thus, articles published after the filing date of the application illustrate the efficacy and beneficial properties of the fully enabled application.

Applicants submit that the application fully enables the claims and requests withdrawal of this rejection under 35 U.S.C. § 112, first paragraph, with respect to claims 1-3, 5-10 and 12-18.

CONCLUSION

Applicants respectfully submit that the claims are in condition for allowance, and notification to that effect is earnestly requested. The Examiner is invited to telephone Applicant's attorney at (516) 795-6820 to facilitate prosecution of this application.

If necessary, please charge any additional fees or credit overpayment to Deposit Account No. 19-0743.

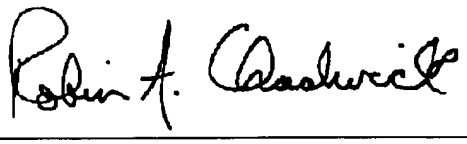
Respectfully submitted,

GENOVEFFA FRANCHINI ET AL.

By their Representatives,

SCHWEGMAN, LUNDBERG, WOESSNER & KLUTH, P.A.
P.O. Box 2938
Minneapolis, MN 55402
(516) 795-6820

Date August 28, 2006

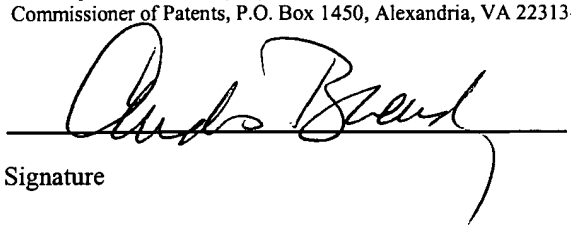
By 

Robin A. Chadwick
Reg. No. 36,477

CERTIFICATE UNDER 37 CFR 1.8: The undersigned hereby certifies that this correspondence is being deposited with the United States Postal Service with sufficient postage as first class mail, in an envelope addressed to: Commissioner of Patents, P.O. Box 1450, Alexandria, VA 22313-1450, on this 28th day of August, 2006.

CANDIS BUENDING

Name



Signature